Distinguishing Familial Chylomicronemia: Diagnostic Pitfalls and Clinical Implications

Poster Code SA1

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BACKGROUND

- Clinical scoring systems, including the North American Familial Chylomicronemia Syndrome (NAFCS)[1] and Moulin,[2] were developed to identify patients for genetic testing for familial chylomicronemia syndrome (FCS), a rare disorder of chylomicron metabolism
- The NAFCS is designed to help identify patients with FCS based on demographics, clinical history, laboratory values, and the absence of secondary factors that may contribute to HTG[1]
- The Moulin score is designed to help distinguish FCS from multifactorial chylomicronemia syndrome (MCS) based on TG history, acute pancreatitis (AP), absence of secondary factors, response to lipid-lowering therapy, and age at symptom onset[2]

Objective

- This study described the distribution of pre-treatment NAFCS and Moulin scores in PALISADE and their association with clinical FCS and AP

METHODS

Study Population

- This analysis included all 75 randomized patients in the Phase 3 PALISADE trial (NCT05089084) of plozasiran in patients with genetically confirmed or clinically diagnosed FCS[3]
- Patients were scored by both the NAFCS and Moulin systems to enable direct comparison
- Screen failures (48 additional patients) were excluded

Data Sources

- Analyses were performed using data drawn from the PALISADE trial database
- Baseline demographic, clinical, laboratory, medication, and medical-history data were used to calculate NAFCS and Moulin scores

NAFCS Scoring Criteria[1]

- Score components included age at hypertriglyceridemia onset, body mass index, AP history, secondary factors contributing to hypertriglyceridemia, laboratory measures, and predefined interaction terms
- Where score components required interpretation because published definitions did not align exactly with available trial variables, clinically reasonable approximations were prespecified
- Participants were categorized according to published thresholds:
  - **Definite FCS** (≥60 points)
  - **Likely FCS** (45-59 points)
  - **Genetic testing recommended** (30-44 points)
  - **Unlikely FCS** (<30 points)

Moulin Scoring Criteria[2]

- Moulin scores were calculated according to the published criteria
- Components included TG history, secondary factors, AP history, abdominal pain, response to lipid-lowering therapy, and age at symptom onset
- Where required variables were unavailable or incompletely captured in PALISADE, prespecified approximations were used
- Participants were categorized using established Moulin score thresholds:
  - **≥10 FCS very likely**
  - **≥9-10 FCS unlikely**
  - **≤8 FCS very unlikely**

Acute Pancreatitis

- Adjudicated AP events occurring during the randomized treatment period were summarized across NAFCS and Moulin score categories
- AP events were adjudicated according to the revised Atlanta criteria by an independent blinded committee
  - **n** = patients with ≥1 adjudicated AP event
  - **events** = total adjudicated AP events

Statistical Analysis

- Participant distributions across score categories and AP event frequencies were summarized for the overall population and for genetically confirmed and clinically diagnosed FCS subgroups

RESULTS

- NAFCS and Moulin classifications were heterogeneous across the PALISADE population
- PALISADE included 44 genetically confirmed patients (59%) and 31 clinically diagnosed patients (41%); Overall, 37 patients (49%) had a prior documented genetic diagnosis, while 34 (45%) qualified based on a history of AP, 76% of whom had recurrent AP[3]

NAFCS Classification

- NAFCS classifications were distributed across the PALISADE population (**Table 1, Figure 1**)
- Patients with NAFCS scores of <45 ("unlikely FCS, but genetic testing suggested") experienced a similar number of AP events as those classified as "definite FCS" (**Table 1**)
- Application of an NAFCS threshold of ≥45 that many payer groups utilize would have classified 46 patients as having likely or definite FCS and would have excluded 29 patients, representing 39% of the PALISADE cohort (**Table 2**)

Among Genetically Confirmed Patients

- Among genetically confirmed patients, 10/44 (23%) had NAFCS scores <45, including 3/44 (7%) with scores <30 **(Table 1)**

Among Clinically Diagnosed Patients

- Among clinically diagnosed patients, 19/31 (61%) had scores <45
- Application of a NAFCS threshold of ≥45 would have excluded 3 of 4 clinically diagnosed patients who experienced an on-study AP event (**Table 2, Figure 2**)
- **Clinically relevant AP events occurred below conventional NAFCS score thresholds; 43% of patients with AP events would not have met NAFCS ≥45 criteria** (**Table 3, 4**)

Moulin Score Classification

- Using the Moulin score, 48 patients (64%) were categorized as very likely FCS and 27 (36%) fell below this threshold

Among Genetically Confirmed Patients

- Among genetically confirmed patients, 12/44 (27%) were not classified as very likely FCS

Among Clinically Diagnosed Patients

- Among clinically diagnosed patients, 15/31 (48%) fell below the threshold
- All four adjudicated on-study AP events in clinically diagnosed patients occurred in those classified as unlikely or very unlikely FCS (**Table 5**)
- **Clinically relevant AP events occurred below conventional Moulin score thresholds; 57% of patients with AP events would not have met Moulin ≥10 criteria (Table 6)**

Key Findings

- NAFCS and Moulin classifications were heterogeneous across the PALISADE study population
- 23% of genetically confirmed patients had NAFCS <45 and 27% fell below the Moulin "very likely FCS" threshold
- 61% of clinically diagnosed patients had NAFCS <45 and 48% fell below the Moulin threshold
- Application of a NAFCS ≥45 threshold would have excluded 39% of PALISADE participants
- Clinically relevant AP events occurred across score categories, including below conventional NAFCS and Moulin thresholds

Table 1. Distribution of NAFCS Score Categories by Diagnostic Subgroup

NAFCS Results	All Patients n (%)	All Patients Patients with AP*	Genetic Cases n (%)	Genetic Cases Patients with AP*	Clinical Cases n (%)	Clinical Cases Patients with AP*
≥60 definite FCS	25 (33%)	3	20 (45%)	2	5 (16%)	1
≥45-59 likely FCS	21 (28%)	1	14 (32%)	1	7 (23%)	0
≥30-44 genetic testing should be considered	13 (17%)	1	7 (16%)	0	6 (19%)	1
<30 unlikely FCS, but genetic testing suggested	16 (21%)	2	3 (7%)	0	13 (42%)	2
Total, N (%)	75 (100%)	7	44 (100%)	3	31 (100%)	4

Based on score calculations as outlined in Hegele et al.[1]

Table 2. PALISADE Participants Above and Below the NAFCS ≥45 Threshold (Payer Utilization Threshold), by Diagnostic Subgroup

NAFCS Results	All Patients n (%)	All Patients Patients with AP*	Genetic Cases n (%)	Genetic Cases Patients with AP*	Clinical Cases n (%)	Clinical Cases Patients with AP*
≥45 likely FCS	46 (61%)	4	34 (77%)	3	12 (39%)	1
<45 unlikely FCS, but genetic testing suggested	29 (39%)	3	10 (23%)	0	19 (61%)	3
Total	75 (100%)	7	44 (100%)	3	31 (100%)	4

NAFCS scores were calculated using the criteria described by Hegele et al.[1]

Table 3. NAFCS Score Categories and On-Study Adjudicated AP Events, by Treatment Assignment and Diagnostic Subgroup

NAFCS Results	All Patients Placebo n=25	All Patients Plozasiran n=50	Genetic Cases Placebo n=14	Genetic Cases Plozasiran n=30	Clinical Cases Placebo n=11	Clinical Cases Plozasiran n=20
≥60 definite FCS, n (%)	10 (40%)	15 (30%)	8 (57%)	12 (40%)	2 (18%)	3 (15%)
Patients with AP,* n	3	0	2	0	1	0
≥45-59 likely FCS, n (%)	8 (32%)	13 (26%)	5 (36%)	9 (30%)	3 (27%)	4 (20%)
Patients with AP,* n	1	0	1	0	0	0
≥30-44 genetic testing should be considered, n (%)	1 (4%)	12 (24%)	1 (7%)	6 (20%)	0 (0%)	6 (30%)
Patients with AP,* n	0	1	0	0	0	1
<30 unlikely FCS, but genetic testing suggested, n (%)	6 (24%)	10 (20%)	0 (0%)	3 (10%)	6 (55%)	7 (35%)
Patients with AP,* n	1	1	0	0	1	1
Total, n (%)	25 (100%)	50 (100%)	14 (100%)	30 (100%)	11 (100%)	20 (100%)
Patients with AP,* n	5	2	3	0	2	2

NAFCS scores were calculated using the criteria described by Hegele et al.[1]

Table 4. PALISADE Participants and Participants With Adjudicated AP Below Selected NAFCS Thresholds

Number of Patients Below Threshold, n (%)	Overall Cohort Patients n=75	Overall Cohort Patients with AP* n=7
<60	50 (67%)	4 (57%)
<45	29 (39%)	3 (43%)
<30	16 (21%)	2 (29%)

NAFCS scores were calculated using the criteria described by Hegele et al.[1]

Table 5. Distribution of Moulin FCS Total-Score Categories by Diagnostic Subgroup

Moulin Results	All Patients n (%)	All Patients Patients with AP*	Genetic Cases n (%)	Genetic Cases Patients with AP*	Clinical Cases n (%)	Clinical Cases Patients with AP*
≥10 FCS very likely	48 (64%)	3	32 (73%)	3	16 (52%)	0
≥9-10 FCS unlikely	16 (21%)	2	7 (16%)	0	9 (29%)	2
≤8 FCS very unlikely	11 (15%)	2	5 (11%)	0	6 (19%)	2
Total	75 (100%)	7	44 (100%)	3	31 (100%)	4

Moulin FCS total scores were calculated using the criteria described by Moulin et al.[2]

Table 6. PALISADE Participants Below the Moulin FCS Total-Score Threshold of 10, by Diagnostic Subgroup

Number of Patients Below Threshold, n (%)	All Patients Patients n=75	All Patients Patients with AP* n=7	Genetic Cases Patients n=44	Genetic Cases Patients with AP* n=3	Clinical Cases Patients n=31	Clinical Cases Patients with AP* n=4
<10 FCS unlikely/ very unlikely	27 (36%)	4 (57%)	12 (27%)	0 (0%)	15 (48%)	4 (100%)

*Patients with adjudicated AP. AP events were positively adjudicated by an independent blinded committee using the revised Atlanta criteria. Values in columns labeled "Participants with AP" represent participants with at least one adjudicated AP event during the randomized treatment period; one participant experienced more than one event. Because AP occurred after randomization and treatment exposure differed across score categories, these counts are descriptive and should not be interpreted as untreated category-specific AP incidence or predictive performance.

Strict FCS-oriented cutoffs systematically exclude clinically meaningful patients

Figure 1. PALISADE Study NAFCS Scores

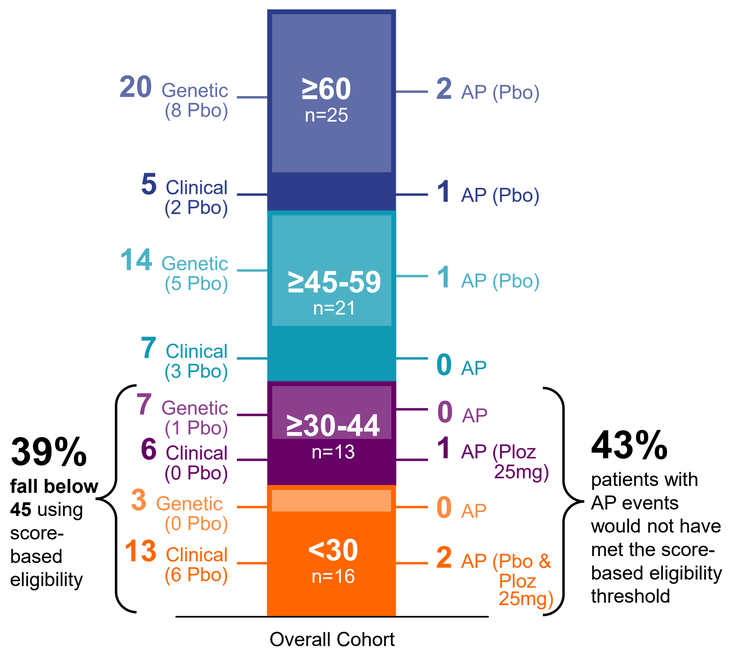


Figure 2. PALISADE Study NAFCS Scores Based on Threshold for High Probability of FCS

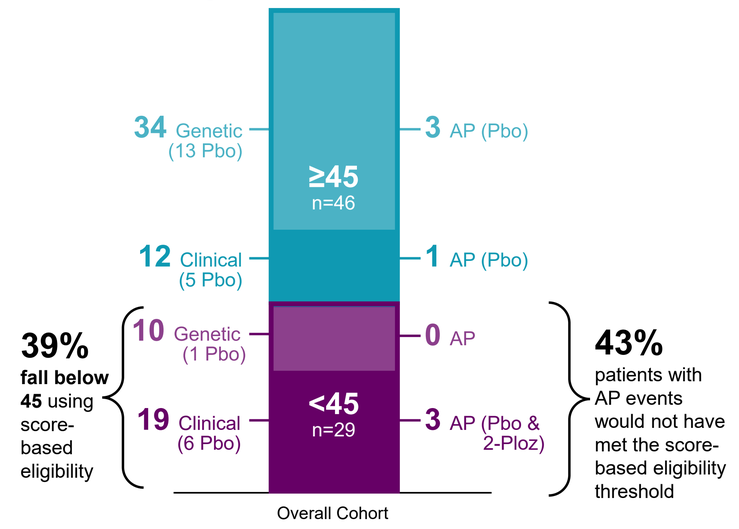
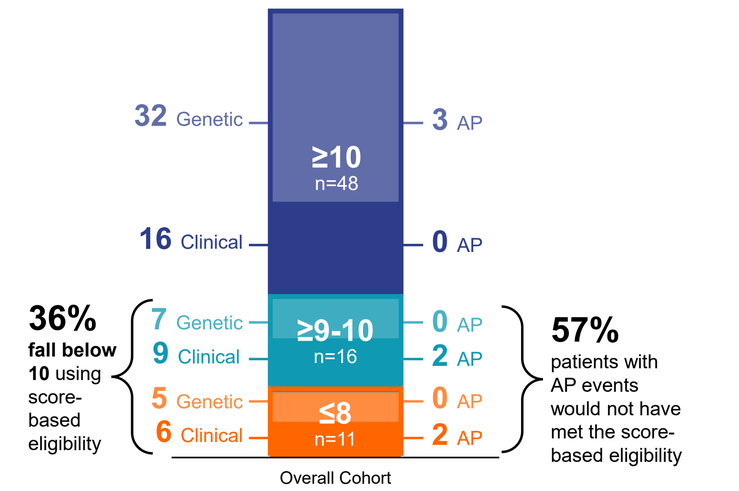


Figure 3. PALISADE Study MOULIN Scores



Traditional Score Thresholds Would Have Missed 43% and 57% of patients who experienced AP using NAFCS and Moulin criteria, respectively.

CONCLUSIONS

- **NAFCS and Moulin scores showed heterogeneity in classifying patients who experienced AP, with clinically relevant events occurring below traditional FCS thresholds, suggesting score-based classification alone may not sufficiently identify patients at risk of AP**
- **PALISADE eligibility criteria, including TG ≥880 mg/dL and history or family history of abdominal pain or AP events, may better capture clinically relevant AP risk**
- **Traditional NAFCS and Moulin cutoffs fail to identify a meaningful proportion of genetically confirmed FCS patients and patients who subsequently experience AP; reliance on these score thresholds alone may under-identify clinically relevant disease**

REFERENCES

1. Hegele RA, et al. *J Clin Lipidol*. 2025;19(1):83–94. **2.** Moulin P, et al. *Atherosclerosis*. 2018;275:265–272. **3.** Watts GF, et al. *N Engl J Med*. 2025;392(2):127–137.

ABBREVIATIONS

AP, acute pancreatitis; **APOA5**, apolipoprotein A5; **APOC2**, apolipoprotein C-II; **APOC3**, apolipoprotein C-III; **FCS**, familial chylomicronemia syndrome; **GPD1**, glycerol-3-phosphate dehydrogenase 1; **GPIHBP1**, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; **HGVS**, Human Genome Variation Society; **LMF1**, lipase maturation factor 1; **LPL**, lipoprotein lipase; **MCS**, multifactorial chylomicronemia syndrome; **NAFCS**, North American Familial Chylomicronemia Syndrome ; **sHTG**, severe hypertriglyceridemia; **TG**, triglyceride; **VLDL**, very-low-density lipoprotein.

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